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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,559	SKOGVALL, STAFFAN	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 18-21* is/are pending in the application.

4a) Of the above claim(s) *5-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/22/02 & 12/14/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an election filed on 7/19/04. There are seventeen claims pending and eight under consideration. Claims 4 and 18-21 are method of using claims. Claims 1-3 are method of making claims. This is the first action on the merits. The application concerns some compositions and uses thereof of the compound RS 67333. RS-67333 appears to be the substance 1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-butyl-4-piperidinyl)-1-propanone.

Election/Restrictions

2. Applicant's election of Group I in the reply filed on 7/11/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 5-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** effective traverse in the reply filed on 7/11/04.

4. Applicant's election of the species RS 67333 is acknowledged. Applicants are advised of MPEP 803.02 Restriction - Markush Claims [R - 2], fourth and fifth paragraph, where is stated:

> "As an example, in the case of an application with a Markush - type claim drawn to the compound C - R, wherein R is a radical

selected from the group consisting of A, B, C, D, and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush - type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush - type claim and claims to the elected species shall be rejected, and claims to the non - elected species would be held withdrawn from further consideration. As in the prevailing practice, **a second action on the rejected claims would be made final.**" (emphasis added).

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is found that anticipates or renders obvious the Markush-type claim with respect to a non-elected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Parts of claims 1-4 and 18-21 are withdrawn from consideration because art was found concerning compositions of RS 67333 (see MPEP 803.02.).

6. Objection is made to claims 1-4 and 18-21 as containing non-elected subject matter. The claimed compositions and methods that employ them present a variable core. These claims contain compounds drawn to the non-elected species.

Specification

7. The incorporation of essential material in the specification by reference to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). The attempt to incorporate subject matter into this application by reference to the thesis "Regeneration of spontaneous tone in guinea pig trachea" by S. Skogvall, Department of Physiological Sciences, Lund University, 1999 is improper because these experimental details would be required by the pharmacologist attempting practice Applicants' assay. In addition, was this thesis ever published?

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. What is RS 67333? In lines 1-13, page 12 of the specification and again in lines 15-23, page 4 of the latest claims, there is a structure followed by the phrase "e.g. preferably RS 67333 and RS 17017". Does Applicant think that the compound pictured is RS 67333 or does he think it is RS 17017? Search of both Chemical Abstracts and the website ChemFinder fails to reveal any mention of RS 67333. The ChemIDplus website gives the name and structure of RS 67333 as 1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-butyl-4-piperidinyl)-1-propanone. Is this the compound whose use is being claimed?

9. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 provides for the use of RS 67333, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-3 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153

USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

10. Claims 1, 3, 4, 19, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Throughout claims 1 and 19, Applicants uses the terms "preferably", "most preferably", and "e.g. preferably". A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

11. Claims 1, 3, 4, 19, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "derivatives" in claims 1 and 19 is indefinite for we do not know which compounds are contemplated. A derivative is the result of a reaction upon an organic molecule. Since we do not know the reagents or the conditions of these reactions, there is no way of determining the structures of the claimed "derivatives". The phrase "derivatives thereof" is, in essence, a product by process claim. Yet Applicants have not described the intended processes sufficiently that we may understand the structures of the compounds they claim. Webster's New World Dictionary defines derivative as "a substance derived from ... another substance by chemical change", and "substitution of one or more elements or radicals for one or more constituents of the original substance" has occurred. All implying that new chemical bonds have formed.

The Examiner suggests deletion of any mention of derivatives.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating asthma with compositions of RS 67333. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The two main issues are the lack of any correlation between clinical efficacy for asthma treatment and Applicants' single *in vitro* assay and the state of the prior art concerning RS 67333 and its' action in inducing constriction of human airways *in vitro*.

There is an *in vitro* assay described in the passage spanning line 24, line 30 to line 16, page 31. Applicants do not state and it is not recognized in the asthma pharmacological arts this assay is correlated to clinical efficacy for treating

asthmatic diseases. Dupont (Respiratory Journal) provides the state of the pharmacological arts in asthma treatment by the compound RS 67333. This reference states that rather than improving asthma, RS 67333 would make the condition worse.

In figure 4, page 646, Dupont (Respiratory Journal) shows a dose dependant contraction of a human airway preparation induced by RS 67333. The data points for RS 67333 are indicated by the triangles. RS 67333 is described as an agonist of 5-HT_4 receptor. In contrast to this observation of the effect of RS 67333 is Figure 3, page 645. Figure 3 shows those antagonists, especially the 5-HT_4 antagonists tropisetron and GR 125478D, alone had no effect on the human airway and that antagonists reduced the contractions caused by 5-HT itself. This is, of course, exactly the behavior expected of an antagonist. Since asthma is produced by a contraction of the airway, agonists like Applicant's elected RS 67333 would increase the airway contraction and make the condition worse in patients suffering from an asthma attack.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue

experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

13. Claims 4 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the 1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-butyl-4-piperidinyl)-1-propanone1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-butyl-4-piperidinyl)-1-propanone compound such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

The factors to be considered in making an enablement rejection have been summarized above. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before asthma symptoms

occur. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage in lines 28-33, page 2 lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical allergic medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become asthmatic before the fact. 6) The artisan using Applicants invention would be a Board Certified physician in immune diseases with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of bronchial diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent asthma generally. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and

physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases..

The Examiner suggests deletion of the word "prevention".

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Clark ('458). The phrase " for therapeutic or prophylactic treatment of disorders *** at least 90%" in claim 1 is a statement of intent. It places no physical limitations upon the claim and is afforded no patentable weight. Claim 1 is a method of making a pharmaceutical composition of the compound RS 67333. The compound 1-(4-amino-5-chloro-2-methoxyphenyl)-3-(1-butyl-4-piperidinyl)-1-propanone is named in claims 2 and 3 of the reference. It has Registry Number 160845-95-4 and synthesis is found in lines 34-37, column 33 of the reference. Preparation of compositions is taught in the reference in lines 15-49, column 11.

Conclusion

15. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

16. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

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TCMcK/me